

REPLY PURSUANT TO 37 C.F.R. § 1.111**REMARKS AND ARGUMENTS**

Claims 10-19 are currently pending in the application. Claims 10-19 are rejected. The Examiner's rejections are respectfully traversed below.

REJECTIONS**Section 3 of the Office Action - Rejection under 35 USC 112, second paragraph:**

Claims 10-19 stand rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the examiner maintains that "no specific definition for Form II was made." Furthermore, the examiner states that "it is unclear "what" does it mean when the claimed scope is being drawn to "Form II of (-)cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-3S-hydroxy-1-methyl]piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate" and questions if it is "a solvate constituting [consisting] of (-)cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-3S-hydroxy-1-methyl]piperidinyl]-4H-1-benzopyran-4-one hydrochloride and solvate or is it a material comprising (-)cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-3S-hydroxy-1-methyl]piperidinyl]-4H-1-benzopyran-4-one and ethanol with allowable "other" elements?" The examiner further notes that "in U.S. 6,576,647 [647] which is commonly assigned, it was defined that "Form II" as distinguished from Form I is that it is an ethanol/hydrate of (-)cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-3S-hydroxy-1-methyl]piperidinyl]-4H-1-benzopyran-4-one hydrochloride, see col. 3 lines 47-50." Finally, the examiner notes that the '647 ethanol/hydrate "Form II" has identical X-ray diffraction pattern and was made by the identical procedure (see columns 6-8, example 4).

Applicant respectfully traverses this rejection for the following reasons:

1. First, Applicant respectfully traverses the allegation that no specific definition for "Form II" was made in the specification. The claimed compound is Form II of (-)cis-

2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate; that is, it is a crystalline form of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate that is identified by its characteristic X-ray diffraction pattern. The specification clearly describes and defines on page 1, lines 26-27, that "the superior solvate form is the Flavopitridol [(-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one] hydrochloride ethanol solvate form (hereinafter "Form II")". Additionally, on page 1, lines 32-33 through page 3, line 8, it is clearly stated that Form II means the ethanol solvate with (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride. Finally, the preparation of Form II as described in Example 1, pages 6-8, clearly concludes with the statement that the procedure gives "the ethanol solvate of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride." Thus, it is respectfully submitted that the specification and claims are clearly and concisely written in art-recognized terminology, and one of ordinary skill in the art clearly and unambiguously understands from the specification and claims that the applicant has defined and claimed "Form II" as (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate.

Furthermore, the specification clearly admits that Form II is hygroscopic (page 4, lines 1-3), and that the "use in a form which is essentially free from water is preferred." Thus, the claimed Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate, identified by its stated characteristic X-ray diffraction pattern, is fully supported by the specification, and the disclosure is unambiguous and clearly understood by one of ordinary skill in the art that other allowable elements are not present.

2. The examiner cites the commonly assigned U.S. '647 patent as defining "that 'Form II' as distinguished from Form I is that it is a ethanol/hydrate (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride, see Col. 3, lines 47-50" and points out that "the '647 ethanol/hydrate has identical X-ray diffraction pattern and was made by the identical procedure (see columns 6-8, example 4).

With respect to claim compliance and the requirement for definiteness of 35 U.S.C. 112, second paragraph, MPEP 2173.02 provides that the definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the particular application disclosure, (2) the teachings of the prior art, and (3) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

The test for definiteness under 35 U.S.C. 112, second paragraph is whether "those skilled in the art would understand what is claimed when the claim is read in light of the specification." [Orthokinetics Inc. v. Safety Travel Chairs, Inc., 806 F.2d 1565, 1576, 1 USPQ2d 1081, 1088 (Fed. Cir. 1986)]. As discussed in paragraph 1 above, the disclosure of the instant application clearly describes, supports, defines and claims Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate, and the disclosure is unambiguous and clear to one of ordinary skill in the art that other allowable elements are not included in the claimed subject matter.

The examiner cites the description of "Form II" in U.S. '647 (col 3, lines 47-50) and questions if applicant's Form II is an ethanol solvate with allowable "other" elements. With respect to prior art rejection of a claim as indefinite, all words in a claim must be considered in judging the patentability of the claim against the prior art [In re Wilson, 424, F.2d 1382, 165 USPQ 494 (CCPA 1970)]. It is unclear if the examiner is attempting to use U.S. '647 as "prior art" or on what grounds the examiner's citation of U.S. '647 is based. It should be appreciated that U.S. '647 and the instant application were each filed on January 16, 2001, and thus the U.S. '647 disclosure cannot be considered as prior art against the instant application.

With respect to U.S. '647, one of ordinary skill in the art further understands by thorough reading of both the instant application and U.S. '647 that different problems are addressed and solved in each instance. The instant application addresses and solves the problem of how to prepare a superior therapeutically useful form of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride as the ethanol solvate (characterized as "Form II"), while U.S. '647

addresses and solves the problem of how to prepare a therapeutically useful form of the anhydrous or solvate free form of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride (characterized as "Form I") from hygroscopic "Form II" material.

Both the instant application and U.S. '647 clearly admit that Form II is hygroscopic, but the problem of drying the hygroscopic Form II is addressed and solved only in U.S. '647. Thus, the description of Form II by the inventors of U.S. '647 takes into account the hygroscopic nature of the Form II material. It is clear to one of ordinary skill in the art that Example 1 of the instant application and Example 4 of U.S. '647 identically teach (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate. It is also clear to one of ordinary skill in the art that Form II is hygroscopic by the hygroscopicity screening data provided in Example 3 of U.S. '647. Finally, the inventors of U.S. '647 discussed Form II in such manner in their specification (col. 3, lines 47-50) so as to clearly convey to one of ordinary skill in the art that Form II may contain subsequently adsorbed moisture due to its hygroscopic properties, and that both water and ethanol are each removed via their process for converting hygroscopic Form II to anhydrous or solvate free Form I. Thorough reading and understanding of the problems addressed and explanations provided by U.S. '647 clearly conveys to those of ordinary skill in the art that:

- a) Form II is identically prepared in both the instant application and U.S. '647,
- b) Form II as obtained in both the instant application and U.S. '647 Example 4 is the ethanol solvate of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride, and
- c) Form II is hygroscopic, and both ethanol and any subsequently adsorbed water are removed from Form II by the claimed disclosure of U.S. '647 to afford the anhydrous or solvate free Form I material.

Thus, from the foregoing, it is respectfully submitted that the issue of the definition of Form II does not exist.

Lastly, claim interpretation based on the disclosure of the instant application by one of ordinary skill in the art at the time the invention was made would be that Form II is an ethanol solvate of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride that can be isolated and

unambiguously characterized by its X-ray diffraction pattern. The compound is clearly named by art-recognized nomenclature, and nothing in the disclosure of the instant application nor the art-recognized nomenclature for Form II implies the presence of additional elements such as water.

In view of the foregoing, applicants respectfully request withdrawal of the rejection to the affected claims.

Section 4 of the Office Action - Rejection under 35 U.S.C. § 102(f)

Claims 10-19 stand rejected under 35 U.S.C. 102(f) as being anticipated by U.S. 6,576,647. The examiner states that "claims 10-19 are directed to the same material owned and disclosed by "another" which is commonly assigned", and that "the priority under 35 U.S.C. 102(g) and possibly 35 U.S.C. 102(f) of this single invention must be resolved." The examiner specifically rejected claims 10-19 under 35 U.S.C. 102(f) as noted above.

Applicant respectfully traverses the rejection based on submission of the attached two declarations under 37 C.F.R. 1.132, and the two page Appendix A that is comprised of a copy of notebook page 53 from Kurt M. Kessler's laboratory notebook KK 28 and a supporting NMR spectrum. In summary, the attached declarations and Appendix A support the following statements:

1. Gary L. Bafus, Christine M. Harrison-Bowman and Gary Lee Silvey, the inventors of U.S. '647, provided a joint declaration under 37 CFR 1.132. Their declaration states that the procedure of example 4 for the preparation of Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate as disclosed but not claimed in U.S. '647 was the procedure of Kurt M. Kessler.
2. Kurt M. Kessler provided an unequivocal declaration under 37 CFR 1.132 that he conceived and reduced to practice the procedure disclosed and claimed in the instant application for the preparation of Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-

one hydrochloride ethanol solvate. Applicant also reaffirms that the inventors of U.S. '647 employed the aforesaid preparation of Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate as starting material for their invention of Form I of anhydrous or solvate free (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride.

3. In support of his declaration, a copy of the signed and witnessed page 53 from Kurt M. Kessler's laboratory notebook KK 28 is provided as the first page of Appendix A. The laboratory notebook page shows Kessler prepared Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate by procedure B that is indicated as a circled B in the left margin of page 53. Page 2 of Appendix A is an NMR spectrum of the product obtained from procedure B on page 53 of the aforesaid notebook that supports the Form II material so obtained is an ethanol solvate. Dates were redacted from both pages of Appendix A to preserve the rights of the inventor.

Based on the foregoing, it is clear that the inventorship of the instant application is correct and that the inventors of U.S. patent 6,576,647 attribute that the procedure of example 4 employed for their preparation of Form II material is according to the procedure conceived and reduced to practice by Kurt M. Kessler.

In view of the foregoing, applicants respectfully request withdrawal of the rejection to the affected claims.

Section 5 of the Office Action - Rejection under 35 U.S.C. § 112, first paragraph

In section 3 of the office action, the examiner states that "if the example 4 of U.S. 6,576,647 is a (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol hydrate as defined at column 3, then claims 10-19 are rejected under 35 U.S.C. 112, first paragraph, as

containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention."

In section 5 of the office action, claims 10-19 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art the inventor(s), at the time the application was filed, had possession of the claimed invention.

The examiner further states that "it is evidenced that in U.S. 6,576,647 which is commonly assigned, a product was defined as 'Form II' as distinguished from Form I is that it is a ethanol/hydrate of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride, see col. 3, lines 47-50. In addition the said '647 disclosed ethanol/hydrate form II has identical X-ray diffraction pattern and was made by the identical procedure (see columns 6-8, example 4). Therefore, no (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate per se was made nor was procedure for making the (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate per se."

In the discussion for Section 3 of this response, applicant clearly established that the instant application unequivocally defines Form II as the ethanol solvate of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride, and that both the instant application (Example 1) and U.S. '647 (Example 4) provide identical methodology for the preparation of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol hydrate. Form II is clearly named by art-recognized nomenclature, and nothing in the nomenclature of Form II in the instant application nor in U.S. '647 Example 4 (which is the starting material for the claimed invention of U.S. '647) implies the presence of additional elements such as water. Both the instant application and U.S. '647 clearly admit that Form II is hygroscopic, but only in U.S. '647 is the problem of preparing an anhydrous or solvate free form of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride (Form I) discussed, addressed and solved. As pointed out in the above discussion of Section 3 of the

office action, the inventors of U.S. '647 discussed Form II in such manner in their specification (col. 3, lines 47-50) so as to clearly convey to one of ordinary skill in the art that Form II is hygroscopic and may contain subsequently adsorbed moisture, and that both water and ethanol are each removed via their process for converting Form II to the anhydrous or solvate free Form I. Thorough reading and understanding of the problems addressed and explanations provided by U.S. '647 clearly conveys to those of ordinary skill in the art that:

- a) Form II is identically prepared in the instant application and in U.S. '647 as the starting material for the claimed Form I invention of U.S. '647,
- b) Form II as obtained in both the instant application and U.S. '647 Example 4 is the ethanol solvate of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride, and
- c) Form II is hygroscopic, and the problem of removing both ethanol and any subsequently adsorbed water from Form II is addressed, discussed and solved by U.S. '647 to afford the anhydrous or solvate free Form I material.

In summary, Form II of (-)-cis-2-(2-chlorophenyl)-5,7-dihydroxy-8-[4R-(3S-hydroxy-1-methyl)piperidinyl]-4H-1-benzopyran-4-one hydrochloride ethanol solvate is defined and described in the instant application in such a way as to reasonably convey to one of ordinary skill in the relevant art that the applicant, at the time the instant application was filed, had possession of the claimed invention.

In view of the foregoing, applicants respectfully request withdrawal of the rejection to the affected claims.

CONCLUSION

Applicants respectfully submit that the claims 10-19 are now in condition for allowance and respectfully requests a notice to this effect. Should the Examiner have any questions please call (collect if necessary) the undersigned agent at the telephone number listed below.

Applicants concurrently submit herewith a petition for a one-month extension of time to make this response timely. The Commissioner is hereby authorized to charge these fees and any other fees that are due to this paper to Deposit Account No. 18-1982 for Aventis Pharmaceuticals Inc., Bridgewater, NJ. Please credit any overpayment to Deposit Account No. 18-1982.

Respectfully submitted,

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